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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/827,495	04/06/2001	Leticia Delgado-Herrera	6688.US.01	5748

23492 7590 05/21/2003

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EXAMINER
BAHAR, MOJDEH

ART UNIT	PAPER NUMBER
1617	15

DATE MAILED: 05/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/827,495	Applicant(s) DELGADO-HERRERA ET AL.	
	Examiner Mojdeh Bahar	Art Unit 1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 & 3-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 5, 2003 has been entered.

Claim 1 and 3-9 are herein examined on the merits,

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-6 and 8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the vitamin D2 and vitamin D3 derivatives disclosed in the specification page 3, line 11-page 4, line 5, does not reasonably provide enablement for other vitamin D2 and vitamin D3 derivatives. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to

consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (Bd Apls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence of absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art

7) the predictability of the art, and

8) the breadth of the claims.

Applicant fails to set forth the criteria that defines neither a "vitamin D2 derivative", nor a "vitamin D3 derivative". Additionally, Applicant fails to provide information allowing the skilled artisan to ascertain these compounds without undue experimentation. In the instant case, only a limited number of "vitamin D2 derivative", or "vitamin D3 derivative" examples are set forth, thereby failing to provide sufficient working examples. It is noted that these examples are neither exhaustive, nor define the class of compounds required. The pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. The instant claims read on all "vitamin D2 derivatives" or a "vitamin D3 derivatives", necessitating an exhaustive search for the embodiments suitable to practice the claimed invention. In order to show the state of the art, applicant's attention is drawn to Bouillon et al., Structure-Function Relationships in the Vitamin D endocrine System. *Endocrine Reviews,* Vol. 16, No. 2, pp.200-257, 1995. Bouillon teaches how different Vitamin D2 and D3 analogs and

derivatives exhibit different biological activity, see for example Table 2. Given the structural variety of vitamin D2 and D3 analog and derivatives as taught by Bouillon and their varied biological profiles, the skilled artisan would need to conduct undue experimentation to ascertain which of these vitamin D2 and D3 analogs and derivatives are suitable for the practice of this invention. Applicants fail to provide information sufficient to practice the claimed invention, absent undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3-6, and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The expressions of "vitamin D2 derivative" and "vitamin D3 derivative" recited in claim 1 render the claims indefinite as to the vitamin D compounds encompassed by the claims. The examiner notes that on page 3 of the instant specification lists a number of vitamin D compounds. However, it is unclear what additional compounds might be also encompassed by the terms "vitamin D2 derivative" and "vitamin D3 derivative". Given the many possible structures of these compounds and their widely different biological activity, it is not clear which of these derivatives are encompassed by the claims. Therefore the metes and bounds of the claims are not clearly delineated.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Knutson et al. (US Patent 5,869,473) and Zemplar monograph (Physicians' Desk Reference, April, 1998, page 478-480), references of record in the previous office action mailed August 14, 2001.

Knutson et al. teaches 1,25-dihydroxy vitamin D3 is useful in a method of increasing serum calcium level and suppressing the parathyroid hormone (PTH) level at a dosage of at least 0.5μg, given 1 to 3 times per week (See particularly col. 3, line 2-24; also col. 5, line 15-col. 6, line 52).

Zemplar monograph teaches that 1,25-dihydroxy-19-nor ergocalciferol is useful in a method of increasing serum calcium level and suppressing PTH level (See particularly page 479, col. 1, Clinical Studies Section, and the second table in col. 2 and 3). Zemplar monograph also teaches that the dosage of 1,25-dihydroxy-19-nor ergocalciferol to be 2.8-7μg (See particularly page 480, col.1, Dosage and Administration Section).

The references do not expressly teach that hypocalcemia in critically ill patient may be manifested as hypocalcemic with elevated parathyroid hormone level and may be treated by 1,25-dihydroxy vitamin D3 or 1,25-dihydroxy-19-nor ergocalciferol herein. The references do not expressly teach the length of therapy to be 1-4 weeks. The references do not expressly teach 1,25-dihydroxy vitamin D3 or 1,25-dihydroxy-19-nor ergocalciferol to be administered daily. The references do not expressly teach the 1,25-dihydroxy vitamin D3 or 1,25-dihydroxy-19-nor

ergocalciferol to be combined with a pharmaceutically acceptable carrier prior to the administration.

It would have been obvious for one of ordinary skill in the art at the time the invention was made to employ 1,25-dihydroxy vitamin D3 or 1,25-dihydroxy-19-nor ergocalciferol daily in a method to treat ICU-associated hypocalcemia for 1-4 weeks.

One of ordinary skill in the art would have been motivated to employ 1,25-dihydroxy vitamin D3 or 1,25-dihydroxy-19-nor ergocalciferol daily in a method to treat ICU-associated hypocalcemia for 1-4 weeks because 1,25-dihydroxy vitamin D3 or 1,25-dihydroxy-19-nor ergocalciferol are known in the art to be useful in a method to treat the symptoms of ICU-associated hypocalcemia (i.e., hypocalcemia and an increased level of PTH). In addition, the optimization of result effective parameters (e.g., dosing frequency, dosing regimens) is obvious as being within the skill of the artisan, absent evidence to the contrary. Furthermore, simply combining the active drugs with a pharmaceutical acceptable carrier (e.g., saline) prior to the administration is within the purview of a skilled artisan, and is therefore obvious.

Response to Arguments

Applicant's arguments filed February 5, 2003 have been fully considered, but are not found persuasive to remove the rejections under 35 UCS 112 and 103 in the previous office action. Applicant first argues that the full scope of the claims is enabled by the instant disclosure. In order to show the state of the art, applicant's attention is drawn to Bouillon et al., Structure-Function Relationships in the Vitamin D endocrine System. *Endocrine Reviews,* Vol. 16, No. 2, pp.200-257, 1995. Bouillon teaches how different Vitamin D2 and D3 analogs and

derivatives exhibit different biological activity, see for example Table 2. Given the structural variety of vitamin D2 and D3 analog and derivatives as taught by Bouillon and their varied biological profiles, the skilled artisan would need to conduct undue experimentation to ascertain which of these vitamin D2 and D3 analogs and derivatives are suitable for the practice of this invention. Applicants fail to provide information sufficient to practice the claimed invention, absent undue experimentation. Applicant then refers to the specification wherein a vitamin D compound is defined: "a vitamin D compound encompasses compounds which control one or more of the vitamin D responsive processes in mammals". Applicant's attention is drawn to the Bouillon article wherein the many different effects of vitamin D and its derivatives are set forth. Given that vitamin D and its derivatives have many different biological activities and structural differences that are responsible for varied biological profiles, the Skilled Artisan cannot ascertain which of these compounds are suitable for the practice of the instant invention.

Applicant's rebuttal arguments averring a distinction between the examiner cited prior art and the instant invention have been considered, but are not found persuasive. Applicant relies on the Table provided on page 4 of the response, arguing that critically-ill patients do not have elevations in PTH and vitamin D deficiency. Applicant then argues that the absence of guidelines for treating ICU related hypocalcemia in Harrison illustrates the novelty of the instant invention. Possessing the examiner cited prior art, and those teachings known to one of ordinary skill in the art, the instant invention would have been obvious at the time of the instant invention was made. Attention is directed to *Harrison's Principles of Internal Medicine*, 13th ed. 1994, pages 2165-2171 setting forth those facts known to one of ordinary skill in the art. Harrison teaches that *hypocalcemia in critically ill patient may be manifested as low calcium level with*

elevated parathyroid hormone (See particularly page 2165, col. 1, last paragraph – col. 2, fourth paragraph and Tables 357-6 and 357-7; page 2168, col. 2, second to last paragraph - page 2170, col. 1, line 2). Harrison also suggests that the *treatment of hypocalcemia may involve vitamin D2 and D3 compounds such as calcifediol and calcitriol* (See page 2170, col. 2 – page 2171, col. 1, last paragraph, Treatment of Hypocalcemia Section).

Applicant has presented a Table on page 2 of the response. Note that it is not clear how this data has been obtained. Is this data compiled by the applicant? Is it the result of applicant's experimentation? Is it from a prior art reference? Note that if this data is presented as a showing of unexpected results of the instant invention, then the data needs to be submitted in proper form, i.e., a declaration under 37 CFR 1.132. Attorney's arguments do not constitute a showing of unexpected results. Further note that the data presented is not clear. It is not understood what a down arrow followed by a right arrow represent. It is applicant's burden to demonstrate unexpected results over the prior art. See MPEP 716.02, also 716.02 (a) - (g). Furthermore, the unexpected results should be demonstrated with evidence that the differences in results are in fact unexpected and unobvious and of both statistical and practical significance. *Ex parte Gelles*, 22 USPQ2d 1318, 1319 (Bd. Pat. App. & Inter. 1992). Moreover, evidence as to any unexpected benefits must be "clear and convincing" *In re Lohr*, 137 USPQ 548 (CCPA 1963), and be of a scope reasonably commensurate with the scope of the subject matter claimed, *In re Linder*, 173 USPQ 356 (CCPA 1972).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mojdeh Bahar whose telephone number is (703) 305-1002. The examiner can normally be reached on Mon to Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Sreeni Padmanabhan, can be reached on (703)-305-1877. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Mojdeh Bahar, J.D.
Patent Examiner
May 16, 2003

SREENI PADMANABHAN
PRIMARY EXAMINER

5/18/03